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The ketogenic diet as a non-pharmacological treatment for HIV-associated neurocognitive disorder: A descriptive analysis

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Abstract

Mitochondrial dysfunction is associated with abnormal glucose metabolism, inflammation and greater oxidative stress in the brain, each of which may contribute uniquely and perhaps synergistically to HIV-Associated Neurocognitive Disorders (HAND) risk. The ketogenic (i.e., low carbohydrate) diet provides the brain with a highly efficient mitochondrial fuel and is associated with improved cognitive performance in older adults with impaired neurocognitive functioning secondary to ageing, Alzheimer's, and Parkinson's disease; however, whether these cognitive gains are generalizable to older adults with HAND is unknown. Thus, the process and cognitive outcomes of the first participant randomized to the intervention and to the control group were investigated in this case-comparison study. To our knowledge, this is first report to establish the plausibility of the ketogenic diet as a treatment for HAND.

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Disclosures

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Keywords

Ketogenic diet; HIV-associated neurocognitive disorder; Aging; Executive function; Speed of processing

Introduction

Despite tremendous reductions in mortality, individuals living with HIV may experience premature and accelerated cognitive decline (i.e., executive function, memory, attention, and speed of processing) in comparison to similar, non-HIV populations. As defined by the Frascati criteria, HIV-Associated Neurocognitive Disorder (HAND) is a spectrum of neurocognitive deficiencies that range in severity (asymptomatic, mild to moderate, and HIV-associated dementia) [1] and affect more than 50% of HIV+ adults over 50 years of age. The early onset of cognitive decline is particularly problematic in those aging with HIV because of the critical role of cognitive function on effective daily task management (e.g., medication adherence, attending medical appointments, and financial management), a relationship observed across the HAND spectrum, including those with asymptomatic HAND [2]. While the precise mechanism(s) of HAND are not fully understood, emerging evidence suggests that the pathophysiology is multifaceted: Persistent low levels of HIV within the neurological system independent of viral load; obesity and cardiovascular correlates associated with changes in brain structure volumes; neurologic adverse effects of cART; an interaction between normative aging processes; and neurodegeneration secondary to the virus [3–5]. Over time, these processes likely contribute independently, and perhaps synergistically, to lessen cognitive reserve and reduce overall brain health in aging adults with HIV.

The adult brain requires a disproportionate large supply of energy in comparison to all other body organs. Impaired glucose uptake in the brain is well-documented in healthy older populations with mild cognitive impairment as well as in persons living with cognitive disorders associated with a more rapid and progressive cognitive decline (i.e., Alzheimer's and Parkinson's disease) [6]. During periods of fasting or carbohydrate restriction, insufficient plasma glucose activates conversion of fatty acids to ketone bodies (i.e., nutritional ketosis, a metabolic state in which the body's energy needs are met via ketone metabolisms in lieu of glucose utilization). Ketone bodies, primarily β-hydroxybutyrate and acetoacetate, are the brain's primary alternative fuel and can supply up to 80% of the organ's energy needs during times of glucose unavailability [7]. Perhaps of greater importance, unlike glucose, the aging brain maintains the ability for normative ketone uptake and metabolism [8,9]. Thus, it appears that the brain's decline in energy metabolism efficacy observed across a range of neurocognitive disorders may be glucose specific.

Polypharmacy is pervasive across older adult populations; however, adults aging with HIV experience greater drug burden in comparison to similar adults without the condition [10]. Thus, non-pharmacological approaches are preferred when treating HAND given the complex multi-system (e.g., hepatic, renal) involvement of cART therapy. Important benefits of pharmacological versus dietary approaches in the management of chronic conditions

include reduced risk of drug interaction(s) as well as potential monetary savings. The ketogenic diet is an approach that may uniquely improve or maintain cognitive function among the aging HIV population. The ketogenic diet restricts carbohydrate consumption to less than 50 grams/day. Limited intake (i.e., glucose) consumption triggers a metabolism shift from glucose to ketones to sustain the body's energy demands. While restricted carbohydrate diets (e.g., ketogenic diet) have been shown to reduce systemic and neural inflammation, improve brain metabolic efficiency, and enhance cognitive performance in other diseases of the brain (i.e., Alzheimer's and Parkinson's disease) [11], the cognitive effects of a ketogenic diet in the context of HIV-associated cognitive impairment is unknown.

Methods

Overview

Two participants from the parent study with cognitive impairment that completed the intervention (n=1) and control (n=1) arm were analyzed by examining pretest-posttest changes in their cognitive performance for this descriptive analysis. As this was a descriptive study of a treatment protocol, causal inferences are limited. The parent study was approved by the University of Alabama at Birmingham (UAB) Institutional Review Board.

Participants

Participants were recruited from the larger parent study. Specifically, potential participants were recruited with flyers and brochures posted at a university HIV/AIDS clinic and were telephone screened to determine eligibility. Eligibility criteria included: (a) age 50+ years, (b) HIV+ for at least one year and prescribed a consistent cART regimen for at least 6 consecutive months, (c) demonstrate effective HIV management (i.e., $CD4^+ > 350$ cells/mm), (d) have no severe neurological comorbidity (e.g., schizophrenia, Alzheimer's disease) (e) able to understand/speak English, (f) not blind or deaf, (g) have stable housing, (h) no preexisting metabolic or renal comorbidity (e.g., diabetes, renal insufficiency (i.e., serum creatinine < 1.3 mg/dL) or renal failure), (i) not using illicit drugs or regularly consuming more than 3 alcoholic drinks per day at time of screen, and have cognitive impairment. Medical inclusion criteria were verified prior to the baseline appointment by an HIV/AIDS clinic staff member from the participant's most recent health maintenance appointment (i.e., review of medications, $CD4^+$, serum creatinine, serum glucose, urine drug screen, and past medical history). Participants were consented during the baseline (pretest) visit.

Instruments

Cognitive impairment

Cognitive impairment was determined by the Modified Telephone Interview for Cognitive Status (TICS-M) during a telephone prescreen interview prior to study enrollment. A TICS-M score </= 26 indicates cognitive impairment (equivalent to a score </= 25 on the validated/widely used Mini Mental Status Exam) [12].

Pre-existing metabolic disorder

To reduce potential confounding effects of undiagnosed diabetes, a standard (i.e., 75-gram dose) oral glucose tolerance test (OGTT), a diagnostic indicator of prediabetes (140 mg/dL – 199 mg/dL) and diabetes (> 200 mg/dL) [13] was completed during the baseline visit. Two individuals were not invited to continue in the study due to OGTT > 200 mg/dL, indicative of diabetes. In addition, OGTT results were shared with the individual's healthcare provider via the procedures outlined in the approved IRB protocol. After OGTT completion, participants were provided a meal prior to additional data collection.

Demographics and health

Basic demographic information (e.g., age, gender, education, housing status, and ethnicity), food insecurity (Food Security Questionnaire) [14], depression (Centers for Epidemiological Studies – Depression scale (CES-D)), [15] and self-report health information (i.e., daily medications) were obtained.

Cognitive battery

The neuropsychological battery consisted of five demographically normed tasks (i.e., Trails A (psychomotor speed), Trails B (executive functioning), Stroop (executive functioning/ inhibition), Digit Symbol Substitution Test (speed of processing) and the Hopkins Verbal Learning Test (verbal memory), that were administered in a fixed order that took about 45 minutes to complete. The tasks were divided into five cognitive domains to reduce the total number of neuropsychological variables in the analysis and for clinical interpretation [16–18]. This division was made a priori, according to standard neuropsychological practice. The neurocognitive battery was completed at baseline and week 12 [19]. Raw scores and normed values (t-scores adjusted for age and education) were provided in Table 1.

Procedure/Treatment

Eligible participants were randomized to either the (1) ketogenic or (2) patient choice diet group. All participants were instructed to maintain baseline-level exercise practices and persons in the control group were advised to continue their normal dietary pattern (i.e., no restrictions). All meals and snacks were provided to the ketogenic diet group by a metabolic kitchen with extensive experience in nutrition research and delivered weekly via a courier in a commercial grade, insulated cooler. Easy to read labels provided proper food storage and preparation instructions as well as identified the day and sequence (breakfast, lunch, or dinner) for consumption. Total energy requirements were estimated using the Harris-Benedict formula [19] with an activity factor of 1.35 * 10%. An additional 10% total daily energy was provided to each ketogenic diet (i.e., intervention) participant to maintain eucaloric (i.e., calorie neutral) conditions given the well-documented heightened energy demand observed in HIV infection independent of viral load [20].

Participants in the ketogenic diet group selected their meals from an 8-day menu rotation. A registered dietician provided nutrition education (i.e., in-person/verbal and written) regarding foods and beverages to avoid (i.e., sugar sweetened beverages, wine, mixed drinks,

chips, pasta, bread, and sweets) as well as identified foods/beverages congruent with nutritional ketosis (i.e., water, diet sodas, liquors, salad, meats, fish, and eggs) for instances when nourishment was consumed outside of the home.

Data analysis

The first participant to complete each group was selected for this report. A simple pre-post comparison of these cases was constructed (Table 1) to observe changes in cognitive performance.

Results

Both cases were African American women 63 to 65 years of age with similar education and income levels. Participants were prescribed the same cART regimen for at least 6 months and did not have AIDS ($CD4^+$ T lymphocyte count > 350 cells/mm3 confirmed from the clinic visit record). The participant in the ketogenic diet group (Case A) exhibited clear cognitive gains, particularly in the domains of executive functioning and speed of processing; while the participant in the patient choice group (Case B) tended to worsen or remain relatively unchanged across the five cognitive domains.

Discussion

Our descriptive analysis supports a stated hypothesis of the parent study: a carbohydrate-restricted diet may represent an effective, non-pharmacological approach to address HIV-associated neurocognitive impairment in older, aging adults with HIV. In this descriptive comparison, executive function (i.e., cognitive abilities such as cognitive flexibility (i.e., task-set switching) as determined by The Trail Making Test Part B demonstrated notable improvement. Specifically, using the raw scores, Case A (intervention) decreased the time to complete Trails B with no errors by 49% from baseline to week 12. In contrast, Case B (control) slightly increased time to complete Trails B as well as increased the total number of errors on Trails B from zero errors at baseline to two errors at week 12. As observed in previous studies among similar populations, it is expected that older, cognitively impaired adults with HIV that consume a restricted carbohydrate diet will demonstrate an improved or stable cognitive performance and that persons that consume a high carbohydrate diet will continue a more rapid cognitive decline in comparison to older adults without HIV.

Given the limitations of a descriptive comparison analysis, it is unclear whether the positive relationship between consumption of a ketogenic diet and improved executive function observed in Case Study A translates to improved quality of life, better HIV treatment adherence, and/or greater ability to function independently. Future diet studies may consider incorporation of health/health promotion (i.e., medication and medical appointment adherence) and quality of life indicators (i.e., housing stability) to better assess translation of study findings to individual-level outcomes.

Our findings are consistent with the limited cognitive literature that have explored efficacy of the ketogenic diet on cognitive function in other conditions hallmarked by neurocognitive decline (e.g., age-related cognitive impairment, Alzheimer’s disease, Parkinson’s disease).

Krikorian and colleagues (2012) compared a six-week very low carbohydrate versus a high carbohydrate diet in older adults with mild to moderate age-related cognitive impairment and observed significant improvement in verbal memory in the KD group only [21]. Similarly, Taylor and associates (2018) conducted a one-group pre/post KD intervention for 12 weeks in adults with Alzheimer's disease and observed cognitive improvement in memory and attention [22]. Using a dietary supplement (i.e., medium-chain triglyceride oil) to achieve ketosis in the only multi-site, double-blind, placebo-controlled trial of 152 older adults with mild to moderate Alzheimer's disease, Henderson and colleagues (2009) also reported significant cognitive improvement as determined by the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-CS), but only in individuals without the apolipoprotein e4 gene, an inherited allele associated with increased Alzheimer's disease risk believed to promote greater deposition of amyloid plaques in the brain [23]. It remains unclear as to why participants with the e4 gene were not benefitted by ketosis in comparison to those without this gene; however, it is plausible that the reduced mitochondrial enzyme capacity observed in persons with the e4 gene reflects a diminished metabolic flexibility. Whether or not the presence of the apolipoprotein e4 gene uniquely interferes with the brain's ability to tap alternative energy pathways in e4 adults is not currently known. Nonetheless, in the context of cognitively impaired HIV adults, this study provides preliminary support that the ketogenic diet may represent a new approach to prevent and/or treat cognitive impairment without adding to the preexisting high pharmacology burden observed in this population [24].

Conclusion

To our knowledge, this descriptive comparative analysis is the first report of an attempt to explore whether the ketogenic diet may represent a feasible, effective intervention to address the well-established cognitive disparity among older adults with HIV. Thus, it is conceivable that the ketogenic diet represents a novel, low-risk intervention capable of reducing cognitive impairment prevalence and severity in a rapidly aging HIV population. Yet, more research is needed on larger samples to establish generalizability of findings.

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Table 1:

Baseline and Posttest Case Comparisons between Treatment Conditions

Variable	Case A (16) Ketogenic Diet	Case B (15) Patient Choice Diet	Comparisons/ Observations
Race/Gender	African American/Female	African American/Female	Similar
Age (years)	65	63	Similar
Education (years)	11	12	Similar
Income	$10,001 – $20,000 USD	$0 – $10,000 USD	Similar
Lifestyle	Non-smoker/Monthly Alcohol Use	Non-smoker/Monthly Alcohol Use	Similar
Food Insecurity	1	2	Case A exhibited food insecurity without hunger. Case B revealed food insecurity with hunger at baseline.
CES-Depression	43	3	Case A exhibited evidence of depression at baseline, Case B did not.
Oral Glucose Tolerance Test	174 mg/dL	128 mg/dL	Case A was glucose intolerant at baseline; Case B was not.
TICS-M	23	25	Similar

Cognitive Variable	Baseline Raw (adj.)	Week 12 Raw (adj.)	Baseline Raw (adj.)	Week 12 Raw (adj.)	Comparisons/Observations
HVLT-R-Verbal Recall	19 (33)	25 (46)	22 (40)	24 (44)	Differential improvement favored Case A by 13 t-score pts.
HVLT-R-Delay Verbal Recall	5 (27)	9 (47)	8 (42)	7 (37)	Differential improvement favored Case A by 20 t-score pts.
HVLT-R-Verbal Recognition Discrimination Index	11 (52)	12 (59)	10 (45)	9 (38)	Differential improvement favored Case A by 7 t-score pts.
Trails A - Psychomotor Speed (sec.)	33.5 (56)	40.0 (59)	46.2 (44)	57.1 (40)	Differential improvement favored Case A by 17 t-score pts.
Trails B - Executive Functioning (sec.)	118.1 (54)	57.5 (71)	128.0 (45)	132.3 (45)	Differential improvement favored Case A by 17 t-score pts.
Stroop Color - Speed of Processing (no. correct)	77 (55)	92 (67)	59 (39)	67 (46)	Differential improvement favored Case A by 12 t-score pts.
Stroop Incongruent - Executive Functioning (t-score)	39 (39)	38 (38)	32 (32)	33 (33)	Similar
DSST-Copy - Psychomotor Speed (sec.)	98.0 (na)	97.3 (na)	142.9 (na)	127.1 (na)	Case B improved by 15.8 seconds.
DSST-Substitution - Executive Functioning (total correct)	59 (60)	63 (64)	42 (40)	44 (43)	Differential improvement favored by case A by 4 t-score points
Total Differential T-score		+ 76		−2	Differential improvement favored Case A by a total of 39 t-score points

Notes: Adj: Adjust for age/education/race when applicable into a t-score; CES-D: Centers for Epidemiological Studies - Depression; DSST: Digit Symbol Substitution Test; HVLT-R: Hopkins Verbal Learning Test - Revised; NA: Not Applicable; NO: Number; SEC: Seconds; TICS-M: Telephone Interview for Cognitive Status-Modified.